Received: 13 April 2021 | Accepted: 24 June 2021

DOI: 10.1111/all.14991

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

EAACI POSITION PAPER

One Health: EAACI Position Paper on coronaviruses at the human-animal interface, with a specific focus on comparative and zoonotic aspects of SARS-Cov-2

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Funding information
The authors would like to thank the European Academy of Allergy and Clinical Immunology (EAACI) for financial support of the sections, interest groups, and working groups enabling the development and publication of this paper.

Abstract

The latest outbreak of a coronavirus disease in 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), evolved into a worldwide pandemic with massive effects on health, quality of life, and economy. Given the short period of time since the outbreak, there are several knowledge gaps on the comparative and zoonotic aspects of this new virus. Within the One Health concept, the current EAACI position paper dwells into the current knowledge on SARS-CoV-2's receptors, symptoms, transmission routes for human and animals living in close vicinity to each other, usefulness of animal models to study this disease and management options to avoid intra- and interspecies transmission. Similar pandemics might appear unexpectedly and more frequently in the near future due to climate change, consumption of exotic foods and drinks, globe-trotter travel possibilities, the growing world population, the decreasing production space, declining room for wildlife and

Abbreviations: ACE2, angiotensin-converting enzyme-2; ACEI, angiotensin-converting enzyme inhibitors; APN, aminopeptidase N; ARB, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; B0AT1, neutral amino acid transporter (SLC6A19); BatCoV-HKU4, bat coronavirus HKU4; BCoV, bovine coronavirus; BSG, basigin; CCoV, canine coronavirus; CD147, cluster of differentiation 147; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; CECoV, canine enteric coronavirus; CoV, coronavirus; COVID, coronavirus-induced disease; CRCoV, canine respiratory coronavirus; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; DIC, disseminated intravascular coagulation; DPP4, dipeptidyl-peptidase 4; EAACI, European Academy of Allergy and Clinical Immunology; ECoV, equine coronavirus; fAPN, feline aminopeptidase-N receptor; FCoV, feline coronavirus; FIP, feline infectious peritonitis; GRADE, grading of recommendations assessment, development, and evaluation; HCoV-HKU1, human coronavirus HKU1; HCoV-OC43, human coronavirus OC43; HLA-1, human leukocyte antigen class I; IBV, infectious bronchitis virus; L-SIGN, Liver/lymph node-specific intercellular adhesion molecule-3-grabbing integrin; MERS, middle east respiratory syndrome; NRP-1, neuropilin-1; OIE, World Organisation for Animal Health; PHEV, porcine hemagglutinating encephalitis virus; RBD, receptor-binding domain; RT-PCR, real-time polymerase chain reaction; S1, spike protein 1; SARS, severe acute respiratory syndrome; TMPRSS2, transmembrane protease serine subtype 2; WHO, World Health Organization.

free-ranging animals, and the changed lifestyle including living very close to animals. Therefore, both the society and the health authorities need to be aware and well prepared for similar future situations, and research needs to focus on prevention and fast development of treatment options (medications, vaccines).

KEYWORDS
companion animals and pets, coronavirus, disease transmission, One Health, (reverse) zoonosis,

1 | INTRODUCTION

In 2019, an outbreak of a new coronavirus (CoV) disease (COVID-19) was reported in China as a cluster of pneumonia cases originating from an unknown source in the city of Wuhan.[1] In the subsequent COVID-19 pandemic, the World Health Organization (WHO) reported 172,630,637 confirmed cases all around the world, including 3,718,683 deaths (as of 4:07pm CEST, 6 June 2021).[2] This new virus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2).[3]

In the past, two other coronaviruses arose, causing pandemic situations (Figure 1): severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2002 in China, and middle east respiratory syndrome coronavirus (MERS-CoV) in 2012 in Saudi Arabia,[4,5] both responsible for less than 1000 deaths.[3,6]

Orthocoronavirinae is a subfamily of *Coronaviridae* (order Nidoviridae) and were divided into four different genera: alpha-, beta-, gamma-, and delta-coronaviruses.[7,8] Coronaviruses are enveloped viruses and their genome consists of single-stranded positive RNA (Figure 2).[7,9] SARS-CoV-1, MERS-CoV, and SARS-CoV-2 all are members of the genera beta-coronavirus,[10] with similar structure of spike-, envelope-, membrane-, and nucleocapsid proteins (Figure 2).[11] Next-generation sequencing of the whole genome of SARS-CoV-2 showed 79% and 50% nucleotide sequence identities to SARS-CoV-1 and MERS-CoV, respectively.[12]

This EAACI position paper summarizes knowledge (published until 7 June 2021) on COVID in different species, with a special emphasis on COVID-19 among humans and animals living in close vicinity. The paper describes receptors, symptoms, susceptibility, potential transmission routes, and management strategies.

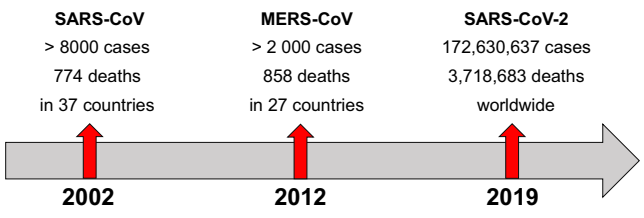

FIGURE 1 Timeline of the three coronaviruses causing pandemic events in the last 20 year.[3,10] Numbers for SARS-CoV-2 taken from the WHO homepage (accessed 6 June 2021)[2]

2 | CORONAVIRUS RECEPTORS AND ASSOCIATED PROTEINS IN HUMAN AND OTHER SPECIES

2.1 | Receptors involved in coronavirus infection in people

The primary receptor for SARS-CoV-2 in humans and several animal species is angiotensin-converting enzyme-2 (ACE2).[13-16] ACE2 is a transmembrane glycoprotein, which physiologically functions as a peptidase, cleaving angiotensin 2 into vasodilator heptapeptide angiotensin-(1–7). The receptor-binding domain (RBD) of the viral envelope spike protein (S) binds to ACE2, independently of its catalytic enzymatic site. The S protein in SARS-CoV-2 has a polybasic furin cleavage site, which enables its cleavage into S1 and S2 subunits, which activates spike proteins and facilitates virus fusion with cellular membranes and entrance to the host cells.[13] Various cellular proteases, such as furin, transmembrane protease serine subtype 2 (TMPRSS2), cathepsin L and B, can cleave the S protein and thus facilitate viral entry into the host cells.[17,18] The cleavage process also provides the C-terminal sequence, which can bind to neuropilin-1 (NRP-1), and provides an additional entrance receptor for SARS-CoV-2.[19,20] Other host proteins stabilize ACE2 structure and prevent its utilization as entry site, for example, B^0AT1, an amino acid transporter in enterocytes.[21] ACE2 in humans is highly expressed in ciliated epithelial cells of respiratory tract, pneumocytes type II, small intestine, endothelial cells, heart, and kidney, but not on innate and adaptive immune cells.[22-25]

Various CoVs can utilize also other host proteins and infect cells that do not express the primary receptor. For SARS-CoV-1 such

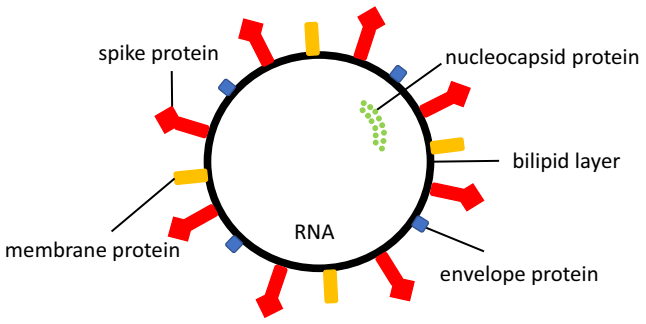

FIGURE 2 Schematic structure of coronaviruses

additional receptors include cluster of differentiation 147 (CD147, basigin, BSG), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), and liver/lymph node-specific intercellular adhesion molecule-3-grabbing integrin (L-SIGN).[26] Each of them has been proposed to serve as an additional receptor for SARS-CoV-2.[27-29] CD147, a transmembrane immunoglobulin-like receptor, forms a membrane complex with many other proteins implicated in the coronavirus-induced pathogenesis, such as cyclophilins A and B, CD44, integrins, and membrane transporters.[30,31] Even if CD147 does not serve as infection entry,[32] it could be responsible for many aberrant immune responses.[33] Moreover, many viruses (including some beta-coronaviruses) use cell surface polysaccharides and sialic acids as cellular attachment co-receptors, resulting in increase of viral particles, and intensification of infection rates.[34] Therefore, cell surface polysaccharides and sialic acids play an important role in pathogenicity and tropism of the CoV and other viruses such as influenza virus in many mammalian species. Sialic acid serves as an additional host receptor for MERS-CoV in humans and camels,[35,36] while the 9-O-acetylated sialic acids facilitate the attachment of bovine Cov (BCoV), human virus OC43 (HCoV-OC43), HCoV-HKU1, and porcine hemagglutinating encephalitis virus (PHEV).[37] Binding to sialic acids and carbohydrates has also been proposed for SARS-CoV-2,[38] yet this requires more studies. SARS-CoV-2 spike protein can also bind to heparan sulfate,[34,39] which is a glycosaminoglycan found in majority of mammalian cells. Also, heparin, widely used as anticoagulant, apparently can bind to SARS-CoV-2 using this mechanism and thus significantly ameliorate the disease.[40] A comprehensive review of coronavirus host cell entry receptors is published by Millet et al[37]

2.2 | ACE2 expression and function in other species

ACE2 from rhesus monkey, Chinese horseshoe bat (*R. sinicus*), Mexican free-tailed bat (*T. brasiliensis*), palm civet, raccoon dog, ferret badger, hog badger, dog, cat, rabbit, and pangolin serve as receptor for SARS-CoV-2 or even for a mutant lacking the cleavage site.[41] ACE2 from humans and rhesus monkey is utilized by SARS-CoV-2 with the highest efficiency. ACE2 from rabbit, pangolin, cat, and dog can support SARS-CoV-2 entry above 50% of the human ACE2 level, with N82 of pangolin ACE2 showing closer contact with RBD than human ACE2.[42] Multiple sequence alignments of the ACE2 proteins show high homology and complete conservation of the five amino acid residues 353-KGDFR-357 with humans, dogs, cats, tigers, minks, and structural remodeling also suggested that the G354H substitution in the surface motif of mink ACE2 increased the binding affinity of the RBD of SARS-CoV-2.[43] Other studies found that "SARS-CoV-2 may not be especially adapted to ACE2 of any of its putative intermediate hosts".[44]

Limited published comparisons of sequences and derived structures of ACE2 in different species resulted in discrepant predictions regarding the susceptibility of horses to SARS-Cov-2 infection, ranging from high risk[45] to low risk.[46]

Due to few nucleotide changes in the RBD[41] mouse and rat ACE2 does not serve as SARS-CoV-2 receptor.

ACE2 is also utilized by SARS-CoV-1 and certain SARS-related bat CoVs (BatCoV-SARSe-WIV1 or BatCoV-SARSr-RaTG13).[37] Other CoVs from different genera utilize various mammalian receptors to infect the host. Several viruses from the alpha-coronavirus genus, responsible for infections in cats, dogs and swine, use the aminopeptidase N (APN, CD13) as the main receptor.[47] Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is used by murine hepatitis virus (MHV) from the beta-coronaviruses genus.[48] MERS-CoV, camel MERS-CoV, and related BatCoV-HKU4 utilize dipeptidyl-peptidase 4 (DPP4) (CD26) as primary receptor.[37,48] DPP4 has been suggested as an entry receptor for SARS-CoV-2 as well.[49,50]

3 | CORONAVIRUSES IN DIFFERENT SPECIES

3.1 | Coronaviruses in human beings

3.1.1 | Clinical manifestations

Most humans are infected by coronaviruses annually, leading to mild symptoms like a common cold. Such infections are caused by human coronaviruses 229E or NL63 (both alpha-viruses), or OC43 and HKU1 (both beta-viruses). In contrast to these mild diseases, SARS-CoV leads to the severe acute respiratory syndrome. The current SARS-CoV-2 was preceded by two more coronavirus epidemics in this millennium: in 2003, SARS coronavirus, now denoted SARS-CoV-1, and another in September 2012, when the WHO reported the first cases of pneumonia caused by the Middle East respiratory syndrome coronavirus (MERS-CoV).[51]

SARS is a respiratory viral disease caused by SARS-CoV-1, with protracted (3–7 days) prodrome, characterized by fever (temperature ≥38°C present in 100% of patients), malaise, headache (39%), and myalgia (49%).[52,53] Unlike other respiratory viral infections, most patients have no upper airways prodrome and start directly with lower airways symptoms at this stage, with a nonproductive cough (66%), which intensifies at the end of prodrome. Subsequently, dyspnea develops (46%), which usually progresses to respiratory failure, requiring mechanical ventilation with progressive pulmonary infiltrates on chest imaging.[53]

MERS-CoV has an incubation period of ca. 5–6 days. Most patients with MERS-CoV infection were adults with severe pneumonia and acute respiratory distress syndrome (ARDS). Some developed acute kidney injury.[54] The most prevalent symptoms include fever (>38°C, 98% of patients), cough (83%), shortness of breath (72%), and myalgias (32%) as well as abnormal chest radiograph (100%). Other clinical manifestations were gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain, and diarrhea), pericarditis, disseminated intravascular coagulation (DIC), and shock.[54]

Patients suffering from COVID-19 experience numerous different symptoms due to organ-specific expression patterns of SARS-CoV-2 receptors (Section 2.1) and immunological changes, some of them applicable for prediction of disease severity.[55] The percentage of patients remaining completely asymptomatic after real-time polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection varies largely, ranging from 1.6% in a Chinese study including 72,314 tested patients to over 50% in two studies including 3711 or 76 patients, respectively.[56] The median incubation period is 5.1 days, and 97.5% of patients show symptoms within 11.5 days after infection.[57] During the early pandemic in spring 2020, fever (88.7% of patients), cough (57.6%), and dyspnea (45.6%) were the most prevalent clinical manifestations.[58] To date, it is well recognized that also upper respiratory symptoms including pharyngodynia, nasal congestion, rhinorrhea, anosmia, or ageusia[59] might appear, preceding the onset of lower airway disease, usually interstitial pneumonia.[60] Fatigue, headache, and myalgia are frequently reported.[61] Gastrointestinal complaints such as nausea, vomiting, or diarrhea are usually experienced, sometimes even prior to fever or lower respiratory tract symptoms.[62] Progression toward the severe and fatal forms include severe pneumonia complicated by ARDS, cardiovascular involvement with cardiac injury, myocarditis, ischemia, cardiac arrhythmias, and DIC.[33] In some cases, COVID-19 was associated with neurological symptoms (acute necrotizing hemorrhagic encephalopathy).[63]

Preexisting comorbidities pose a special risk for accelerated progress of disease and development of ARDS, multi-organ failure, and high mortality. Male gender and an age above 65 are risk factors for more severe COVID-19 disease and inpatient admission.[64] In developed countries, a disproportionally higher morbidity and mortality were reported for non-caucasians, with socioeconomic deprivation as an explanation besides genetic factors.[65]

Type 2 diabetes patients, usually at advanced age, with hyperlipidemia, obesity, hypertension, renal and/or cardiovascular and/or hepatic disease had similar poor outcome.[66,67] The underlying chronic inflammation in these diseases facilitates the development of a virulent cytokine storm. End-stage renal disease[68] and associated anemia were also reported risk factors,[64] together with chronic lung diseases (with the exception of asthma), smoking, pulmonary, and hematologic malignancies.[69-71]

Among the pediatric population, more adolescents with comorbidities develop ARDS.[72]

Surprisingly, there was no increased prevalence in allergic patients (details in supplement and in compendium[73]).

3.2 | Coronaviruses in selected animal species with close contact to humans

3.2.1 | Coronaviruses in cats

Clinical manifestations

Feline coronavirus (FCoV), an alpha-coronavirus, is a common but generally harmless coronavirus,[74] that however sometimes causes the fatal disease feline infectious peritonitis (FIP).[75,76] FCoV is extremely common in the cat population worldwide, especially in multi-cat environments, with up to 80% of cats in catteries being infected.[77] FCoV is transmitted by fecal-oral route between felids, but is not infectious for other species (including humans). FCoV usually does not cause clinical signs, and only rarely is considered responsible for transient and mild diarrhea.[78] As mentioned, sporadically, in about 5% of FCoV-infected cats in multi-cat environments, FIP occurs,[79] a fatal disease if untreated, with a median survival time of 8 days,[80] and the most common infectious cause of death in cats. FIP develops after spontaneous mutations of the genome of the less virulent FCoV within infected cats.[81] Mainly mutations of the spike gene are considered responsible for the switch in pathogenicity.[82] These mutations allow for successful virus replication in macrophages,[83] which is the key event in FIP pathogenesis,[84] leading to an immune-mediated reaction with overproduction of pro-inflammatory cytokines[85] resulting in (peri-)vasculitis and granulomatous lesions in various organs, such as central nervous system, eyes, and parenchymatous organs.[86] Vasculitis leads to fluid accumulation in body cavities, including pleural space, peritoneum, and pericardium. Thus, the clinical picture of FIP varies considerably, reflecting the variability in the distribution of vasculitis and granulomatous lesions combined with non-specific clinical signs, such as lethargy, anorexia, and weight loss.[75] Furthermore, uveitis, hyphaema, change of color of the iris, keratic precipitate or reversed D-shape of pupils can occur in FIP.[87]

Despite the high divergence between feline coronaviruses and SARS-CoV-2,[88,89] cats can get infected with SARS-CoV-2,[90] become RT-PCR-positive, shed the virus, and develop antibodies. Under natural conditions (details Supporting Information), domestic cats as well as tigers and lions tested positive for SARS-CoV-2.[91] Cats infected in the field usually stay healthy, and if clinical signs are detected they are likely caused by unrelated comorbidities. Several reports of SARS-CoV-2-infected cats, that were presumably or definitively infected from SARS-CoV-2-infected humans, have been published from different countries (updated list at OIE[92]). In most of the cases, cats were infected by their owners, but there is also evidence of mink-to-cat transmission. The question whether cats with pre-existing metabolic, pulmonary, neuronal, or cardiovascular diseases are more prone to infection remains to be studied. Some of the medications described as potential risk factors in humans are also used in veterinary medicine, including ACE inhibitors (ACEI)[93] or angiotensin receptor blockers (ARB),[94] but there are no data so far that these medication would influence the outcome of SARS-CoV-2 infection, neither in human nor in feline patients. Concerning the prevalence of SARS-CoV-2 infection in the general cat population, a study in USA testing swabs (over 5000 feline, canine, and equine samples) by RT-PCR for SARS-CoV-2 did not detect positive cats.[95] In a Chinese study, 15 out of 102 (14.7%) cat sera collected following the outbreak in Wuhan tested positive for antibodies against the RBD, 11 cats having neutralizing antibody-titers ranging from 20 to 1080. In 2 cats monitored over 130 days, serum antibodies peaked 10 days after first sampling and declined below detection

limit within 110 days.[96] In the Netherlands, 2 out of 500 evaluated cats (0.4%) had anti-RBD antibodies.[97] In a large-scale study including 817 companion animals in Northern Italy at a time of frequent human infections, no cat tested RT-PCR-positive, but 3.9% of cats had anti-RBD antibodies.[98] In France, among 20 students (2 out of 20 testing positive for SARS-CoV-2 RNA, with 11 out of 18 with symptoms of COVID-19), none of the 9 cats living in the community tested positive for RNA or antibodies.[99] In Rio de Janeiro, 39 pets (29 dogs and 10 cats) of 21 patients were tested, where 9 dogs (31%) and 4 cats (40%) from 10 (47.6%) households were infected with or seropositive for SARS-CoV-2; the study also showed that neutering and sharing of bed posed the highest risk factors for pet infection.[100]

Receptors involved in coronavirus infection in feline species

FCoV can be classified based on differences in antigenic and genomic properties in type I FCoV (more common worldwide) and type II FCoV. Both type I and type II FCoV can occur as less virulent FCoV and as FIP-associated FCoV. Type II FCoV results from double recombination between type I FCoV and canine enteric coronavirus (CECoV).[101,102] Type II FCoV uses the feline aminopeptidase-N receptor (fAPN) present on the intestinal villi and the monocyte.[103,104] The receptor for type I FCoV remains unknown,[104,105] but FIPV I infection of monocytes depends on fDC-SIGN.[106]

Management/treatment in feline species

No effective treatment was available (so every cat with FIP died) until recently when specific antiviral compounds showed intense promise. The most promising compound, GS-441524, is not only effective *in vitro* and in experimentally induced FIP, it also was shown to cure cats with FIP in the field.[107-109] GS-441524 is the active derivative of remdesivir, which together with medications for treatment of Hepatitis C virus has shown promising results also in treatment of COVID-19 in humans.[110]

One intranasal vaccine against FIP is commercially available in the USA and some European countries. It contains a temperature-sensitive mutant of the type II FCoV. The efficacy of this vaccine has been questioned and expert groups generally do not recommend its use.[75] Early experiments using vaccines based on canine coronaviruses or porcine coronaviruses (transmissible gastroenteritis virus, TGEV) did not provide protection but induced antibody-dependent enhancement (ADE).[111] ADE was also observed after experimental infections in cats with pre-existing antibodies against the S protein resulting in a more rapid disease course and earlier death.[112] This enhancement was observed irrespective of whether cats had acquired antibodies through passive or active immunization using some experimental vaccines.[113,114] However, ADE, a feature of some experimental vaccine trials,[115-117] in which more vaccinated cats than control cats developed FIP, has not been observed in field studies, suggesting that the vaccine that is currently on the market does not cause ADE.[118-120] Since FCoV is transmitted predominantly via fecal-oral route and infection is maintained in a household by continual cycles of infection and re-infection,[121,122] hygiene is the mainstay of FIP control in any multi-cat environment.

3.2.2 | Coronaviruses in dogs

Symptoms

Two coronaviruses are commonly found in dogs, CECoV (an alpha-coronaviruses) and canine respiratory coronavirus (CRCoV) (a beta-coronavirus).[74] CECoV is widespread in the dog population, primarily in kennels and shelters. Infection is usually asymptomatic,[123] and if clinical signs occur they are restricted to the gastrointestinal tract with signs of acute appetite loss, vomiting, diarrhea, and dehydration. Clinical importance of CECoV as a pathogen is unclear, since many clinically healthy dogs shed CECoV. Changes in virulence and tissue tropisms through genetic variations are discussed as reasons for outbreaks of clinical disease,[124] and even highly virulent CECoV strains (pantropic canine CoV, CCoV) have been sporadically reported causing fatal systemic disease in puppies.[125]

CRCoV was first identified in the respiratory tract of kennel-housed dogs with respiratory disease.[126] CRCoV is very closely related to bovine coronavirus (BCoV),[126] and cross-species transmission from cattle to dogs has been suggested.[127] CRCoV is detected worldwide with antibody prevalence of up to 60% in the general dog population and presence of RNA in the lower respiratory tract in 1%–27% dogs with respiratory disease. CRCoV can be responsible for mild respiratory signs and is one of the etiological agents of the canine infectious respiratory disease (CIRD) complex.[128,129] The true role of CRCoV as primary single pathogen is not completely clear,[128] but its replication in the respiratory epithelium can damage the mucociliary system[129] leading to a more severe clinical course of infections caused by other respiratory pathogens.

Dogs also can get infected with SARS-CoV-2,[90] become RT-PCR-positive, shed the virus, and develop antibodies; however, dogs are less susceptible than cats and virus shedding is less common. Under natural conditions (details in Supporting Information), several dogs in the field-tested positive for SARS-CoV-2 infection.[91] These dogs usually stay healthy, and if clinical signs are detected they are likely caused by unrelated disease problems. Several reports of SARS-CoV-2-positive dogs that were presumably or definitively infected from SARS-CoV-2-infected humans have been published from several different countries (updated list[92]). In most of the cases, dogs were infected by their owners. Concerning the prevalence of SARS-CoV-2 infection in the general dog population, a study in USA testing swabs (over 5000 canine, feline, and equine samples) by RT-PCR for SARS-CoV-2 did not detect positive dogs.[95] In the Netherlands, 1 out of 500 dogs (0.2%) had anti-RBD antibodies.[97] In a large-scale study including 817 companion animals in Northern Italy at a time of frequent human infections, no dog tested RT-PCR-positive, but 3.4% of dogs had anti-RBD antibodies.[98] Dogs from households with COVID-19 patients were significantly more likely to be antibody-positive than those from COVID-19-negative households. In France, among 20 students (2 out of 20 testing positive for SARS-CoV-2 RNA, with 11 out of 18 with symptoms of COVID-19), none of the 12 dogs living in the community tested positive for RNA or antibodies.[99]

Receptors involved in coronavirus infection in canine species

CECoV uses aminopeptidase-N as receptor.[103] CRCoV, like BCoV, binds to the cell surface via sialic acids (preferentially to α-2,3-linked sialic acids rather than α-2,6-linked sialic acids), and leukocyte antigen class I (HLA-1) molecules serve as entry receptors.[130]

Management/treatment in canine species

Treatment for both, CECoV and CRCoV, is only necessary if the dog has clinical signs. Symptomatic treatment usually leads to complete cure. Antiviral treatment is not recommended.

Inactivated and modified live virus vaccines are available for CECoV in the USA (but not in Europe). Their usefulness has been questioned, because they only provide incomplete protection,[131] do likely not protect against pantropic CCoV,[132] and because CECoV usually causes no or only mild clinical signs. A vaccine against CRCoV is not available.

3.2.3 | Coronavirues in avian species

Symptoms

The avian infectious bronchitis virus (IBV) belongs to genus gammacoronaviruses, being a single-stranded, and positive-sense RNA virus.[133-135] This extremely contagious disease causes serious economic losses worldwide in the poultry industry affecting meat-type (broilers) and egg-laying birds (layers).[136,137] The respiratory and reproductive tract are affected, together with the renal system due to the broad tissue tropism of galliform and non-galliform birds for the IBV, causing morbidity up to 100%. Mortality is low but can reach 50% with some strains that cause nephritis or when opportunistic pathogens, for example, *Escherichia coli* complicate the disease.[133,136,138-142] The economic impact includes decreased egg production, reduced hatchability in breeders, poor external, and internal egg quality in layers as well in breeders, retarded growth, poor carcass weight, and increased condemnation rates in broilers.[133,134,137,138] When affected with damage of the reproductive tract, in young pullets (layers and breeders) failure of production can occur.[133,136,138] IBV has an incubation period of 24 to 48 hours, and the virus spreads rapidly among chickens in a flock via aerosol and mechanical routes. IBV is shedded in feces and nasal secretions.[133-138]

Currently, avian species and poultry unlikely play a role as reservoir, host, or in transmission of either SARS-CoV-2 or MERS-CoV.[143]

Receptors involved in coronavirus infection in avian species

The IBV receptor-binding domain (RBD) in the surface S1-spike glycoprotein is most important for the attachment to host cells.[138-142,144] Variation in S1-glycoprotein partly influences tissue tropism, virulence, and virus entry.[138,141,142] IBV infects trachea, kidney, and the reproductive tract through interaction of the S1-glycoproteins RBD with α-2,3-linked sialic acid receptors on the cell surface.[133,138,141,142]

Management/treatment in avian species

Different serotypes and genetic types of IBV have been identified worldwide and mostly do not cross-protect.[136-140,144,145] Moreover, new variant types of the viruses continue to arise due to mutations and recombinations in the viral genome, making this virus difficult to identify by the immune system and to control via regular vaccination program.[136-139,142]

Epidemiological surveillance, strict biosecurity, and hygienic measures improved knowledge on the circulating and newly emerging field variants of IBV, and vaccines effective against various serotypes are necessary for better control and prevention of IBV in chickens.[134,136-138,144,145] Both live attenuated and killed vaccines are used to control IBV in commercial poultry farms.[137,138,140-142,144-146] Since serotypes of IBV do not cross-protect, genotypes responsible for field infection should be detected and if available, attenuated strains homolog to field strains is an ideal strategy. If homolog-vaccine strains are not available, multivalent vaccine containing two or more antigenic types (classic and variant strains) would be beneficial in providing broad protection (the protectotype concept).[135-137,140,141,144,145]

3.2.4 | Coronaviruses in cattle

Symptoms

Bovine coronavirus (BCoV) belongs to the genus "beta-coronavirus" of the Coronaviridae family. BCoV classified in Group 2 appears specific to the bovine species.[147-149] Wild ruminants, sheep, and goats can become infected by cattle BCoV.[148-151] BCoV causes digestive and respiratory disease due to tissue tropism in young and adult cattle, and was first identified as the agent of severe diarrhea in neonatal calves (neonatal calf diarrhea), as well as in adult cattle (winter dysentery).[147-149,151-157] The respiratory syndrome is frequently observed during or after transportation because the shipping of cattle represents a stress factor that can facilitate the onset of BCoV-induced respiratory disease (shipping fever), mainly in feedlot calves.[147,149,151] Considerable milk losses may be observed in a herd affected by winter dysentery.[148,153] Only one serotype has been identified among BCoV isolates, but some antigenic and genetic differences have been observed between isolates.[148,153] The incubation period in young calves is estimated to be 24–48 hours, and clinical signs usually occur after five days of age, when the level of maternal virus-specific colostrum-derived antibodies decreases in the digestive tract of the calf.[148] The morbidity rate is high, varying between 50 and 100%, and the mortality rate varies according to the level of maternally or actively derived antibodies and the severity of dehydration.[148,153,154] BCoV shedding occurs in feces and nasal secretions.[147-149,157]

For SARS-CoV-2, under experimental conditions, cattle show low susceptibility, and there was no intraspecies transmission to in-contact infection observed.[158] Therefore, there is no indication that cattle play a role in the human pandemic, and no reports of naturally infected bovines exist to date.

Receptors involved in coronavirus infection in bovine species

BCoV is an enteric/respiratory virus, using the 9–0-acetylated sialic acid as a receptor to infect cultured cells.[149,151,156] The initiation of a BCoV infection possibly involves the recognition of different types of receptors: an initial receptor for primary attachment and a second facilitating the fusion between the viral envelope spike (S) protein and the membrane of the host cell.[149-151,155]

Management/treatment in bovine species

The symptomatic treatment is directed against the dehydration and acid-base disequilibrium, which follows the diarrhea.[152] Prevention of infection is based on biosecurity, sanitary, and medical measures.[152] Clinical signs can be reduced by following sound husbandry rules.[152,153,157,159] The preferred strategy is vaccination of the mother with live and inactivated vaccines to enrich the maternal colostrum with specific antibodies against BCoV.[150,152,159]

3.2.5 | Coronaviruses in horses

Symptoms

Equine coronavirus (ECoV) is a beta-coronavirus phylogenetically related to BCoV, human coronavirus OC43, and porcine hemagglutinating encephalomyelitis virus. It is an emerging virus, first isolated and characterized in 2000,[160] although sporadic observations of coronavirus-like particles by electron microscopy have been reported since 1970s.[161-163] Since its isolation, increasing numbers of sporadic cases and outbreaks in adult sports and show horses have been reported in the USA, Japan, and Europe.[164-167] Epidemiologic data suggest fecal-oral route of transmission, confirmed by experimental infection.[168] Most frequent clinical signs include fever, anorexia, lethargy, and colic.[169] Neurological signs have also been observed.[170]

There is no evidence that SARS-CoV-2 can infect or cause a disease in horses, or that they could transmit the virus to other species.

Receptors involved in coronavirus infection in equine species

Limited published comparisons of sequences and derived structures of ACE2 in different species resulted in discrepant predictions regarding the susceptibility of horses to SARS-CoV-2 infection, ranging from high risk[45] to low risk.[46]

Management/treatment in equine species

Most horses recover spontaneously. Those with persistent fever and anorexia are treated with anti-inflammatory drugs. More intensive treatment with intravenous fluids is needed for horses with colic or diarrhea.[171] Prevention of ECoV infection was tested using BCoV vaccine in horses to induce antibodies against ECoV, but it has not been shown to be protective.[172]

3.2.6 | Coronaviruses in pigs

Symptoms

Coronaviruses from three genera have been identified in pigs: *Alphacoronavirus* (porcine epidemic diarrhea virus (PEDV), transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCV) and severe acute diarrhea syndrome virus (SADS-CoV), *Betacoronavirus* (porcine hemagglutinating encephalomyelitis virus (PHEV)), and *Deltacoronavirus* (porcine deltacoronavirus (PDCoV)). TGEV, PEDV, PDCoV, and SADS-CoV cause gastrointestinal infections, PRCV is associated with respiratory infection and PHEV can cause encephalomyelitis or wasting disease in piglets lacking maternal antibodies.[173] PRCV emerged in 1984 as a spike deletion mutant of TGEV and rapidly spread within the population making the pigs immune to both PRCV and TGEV. PDCoV and SADS-CoV have recently emerged in China and are highly homologous with avian or bat coronaviruses, respectively.[173] Enteric coronaviruses (TGEV, PEDV, and PDCoV) are highly contagious (morbidity 100%), cause gastroenteritis with diarrhea and vomiting, which results in dehydration and death (up to 100% mortality). Strong immune responses following natural infection protect against subsequent homologous challenge; however, these viruses display no cross-protection.

There is no evidence of natural infection or disease caused by SARS-Cov-2 in pigs. Attempts to infect pigs yielded conflicting results, mostly showing that pigs are not susceptible,[174,175] but a recent study could detect virus RNA in some pigs after oronasal inoculation of $1x10^6$ PFU.[176] Some of these pigs also showed mild symptoms, such as ocular or nasal discharge. One pig also developed cough and from submandibular lymph node of this pig live virus could be isolated.

Receptors involved in coronavirus infection in pigs

Aminopeptidase N is the major receptor for porcine coronaviruses. It has been shown that SARS-Cov-2 can use porcine ACE2 to enter HeLa cells expressing this receptor.[177] A BLAST query predicted 98% coverage and 81% identity between human and porcine ACE2.[176]

Management/treatment in pigs

Treatment of affected newborn piglets is usually ineffective. In piglets older than 1 week, electrolyte/glucose supplementation may reduce mortality. Enhanced biosecurity measures should be maintained to decrease a chance of introduction of infected animals and contaminated vehicles from TGEV-affected farms to susceptible herds. Protection of piglets can be achieved by vaccination of sows to induce lactogenic immunity.[173]

3.2.7 | Coronaviruses in camelid species

Known from the past Middle East respiratory syndrome (MERS) pandemic, camelids, specifically dromedaries, can be infected with MERS and are able to transmit the virus to humans.[178] In case of SARS-CoV-2, camelids are believed to have a low virus susceptibility, with an ACE2-receptor similarity of 83.25% to humans.[179] There is no evidence, that they can transmit SARS-CoV-2 to people by now.

3.2.8 | Coronaviruses in mustelid species

American mink and ferret are the only mustelid species for which evidence both from experimental and field studies for susceptibility to SARS-CoV-2 is available. Minks are among the most susceptible species.[180] There are no other experimental studies available for other wild mustelid species.

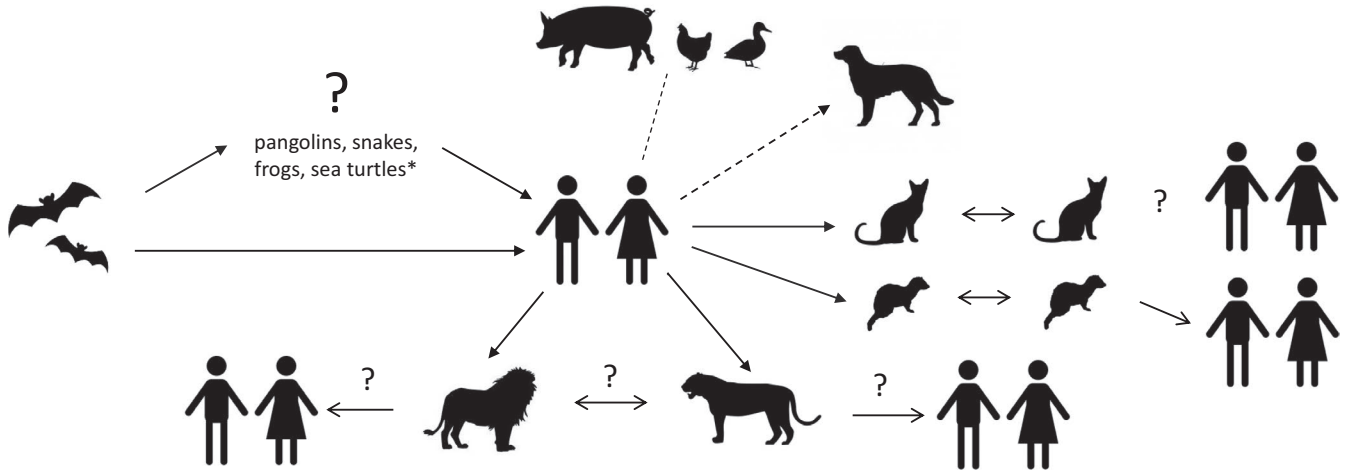

FIGURE 3 Transmission routes of SARS-CoV-2. *, possible intermediate hosts; <->, intra-species transmission; ?, still under investigation; ---, no susceptibility; -->, low susceptibility; ->, high susceptibility

TABLE 1 Origin and (potential) intermediate hosts of SARS-CoV-1, MERS-CoV, and SARS-CoV-2

VIRUS	ORIGIN	INTERMEDIATE HOST	REFERENCES
SARS-CoV-1	Bat	Himalayan palm civet cat, or raccoon dog	16,192-194,216
MERS-CoV	Bat	Dromedary camels	16,192,193,217
SARS-CoV-2	bat*	Pangolins*, snakes (Chinese krait and cobra snakes)*, frogs*, (sea) turtles*	16,192,218,219

*under investigation.

4 | ANIMAL MODELS FOR STUDYING SARS-COV-2 SUSCEPTIBILITY, MECHANISMS, AND TREATMENT OPTIONS

Many studies tried to establish a suitable animal model for the SARS-CoV-2 infection;[181] however, no ideal matching model was found.[182] Due to the entry receptor similarity, great apes and primates (rhesus macaques) seem to be most suitable, as they get infected, spread the virus, and show symptoms.[46,174,183] Non-human primates display virus replication in the upper and lower respiratory tract and in the gastrointestinal tract, and develop pneumonia with bilateral lung involvement, ground-glass opacities, focal edema, and inflammation. Neutralizing antibodies, T-cell immunity, and pro-inflammatory cytokines were shown in infected animals. However, important aspects of the human SARS-CoV-2 infection like specific clinical signs (fever, nasal discharge, and dyspnea), transmission, and gender-specific differences could not be reproduced in non-human primates.[181] Mice are not suitable, but Syrian gold hamsters could be a proper model for SARS-CoV-2 as well as other viruses.[184,185] Hamsters and ferrets are the only animals who display clinical signs.[181] Further, ferrets are especially useful to test vaccines and medication for the upper respiratory tract.[181,186] Although both cats and dogs can get infected, they usually do not develop clinical disease under experimental or natural conditions. Six kittens were challenged in an experimental study with SARS-CoV-2 via intranasal and oral routes simultaneously,[174,187-190] and viral RNA was not detected in blood, but it was present in nasal, oropharyngeal and rectal swabs, bronchoalveolar lavage fluid. Viral RNA and antigen were detected in inflamed tissues of submucosal glands. One day post-challenge, two sentinel cats were commingled with the infected animals. Sentinel cats got infected within two days. All cats remained asymptomatic. Both principal and sentinel cats developed antibodies.[187]

To sum it up, no perfectly suitable or ethically justifiable animal model is currently available. Therefore, it is important that research and development should keep focusing on human clinical trials to find a cure and preventive measure for human coronavirus infections.

5 | ORIGIN AND TRANSMISSION

The One Health movement introduced the concept that people and their animals share the environment, including infections, pollution, food, lifestyle, and increased life expectancy. In this shared scenario, not only the unidirectional (zoonotic),[3,191] but the bidirectional transmission (reverse zoonosis) of SARS-CoV-2 virus can be envisaged. The transmission route and potential origin-host-interactions are important aspects to consider for primary and secondary prevention of infectious diseases (Figure 3). For the novel SARS-CoV-2, genetic analyses showed a high similarity with a coronavirus carried by bats (Table 1). SARS-CoV-1 and MERS-CoV originated in bats and it is likely that they are the natural host of SARS-CoV-2 too.[192-196]

While at the onset of the SARS-CoV-2 pandemic, transmission from animals to humans was in focus, many other reports of naturally infected cats and dogs revealed that SARS-CoV-2 can be transmitted from infected humans to animals. There is also evidence of human-to-non-domestic felid transmission, as the case of a New

York zoo showed, where in April 2020 it was reported that five tigers and three lions of the Wildlife Conservation Society's Bronx Zoo had developed respiratory signs.[197] In the Netherlands and Denmark, SARS-CoV-2 outbreaks have occurred in 17 mink farms in which human-to-mink, mink-to-human, and mink-to-cat/dog transmission occurred.[198-201]

5.1 | Intra-species transmission of SARS-CoV-2

For SARS-CoV-2, respiratory transmission is the most important route.[202] Spreading of respiratory viruses usually happens from person to person per droplets, fomites, or aerosols.[202,203] The effective reproduction rate for SARS-CoV-2 was found to be very high until May 2020, with one person infecting 3 (range 2.5–3.6) other people, positioning COVID-19 as a highly contagious disease.[204] For SARS-CoV-1 and MERS-CoV, fecal-oral transmission is also important. Since SARS-CoV-2 can be found in stool samples, this route could be relevant also for SARS-CoV-2.[203,205-207]

A study compared the structural features of ACE2 receptors in vertebrates, to estimate the risk of other species to get infected by SARS-CoV-2.[46] Susceptibility of different species is considered to be low or moderate (Table 2**)**. Great apes show a high similarity with humans in their ACE2 receptors, therefore, are categorized as very susceptible. Beside the receptor similarity, the risk of SARS-CoV-2 infection also depends on host-specific protease expression, driving the spike protein activation.[186]

Cat-to-cat transmission was demonstrated[174,187,208] (uninfected cats co-housed with infected cats develop antibodies[187,208]), and a very high rate of intraspecies transmission was described in minks.

5.2 | Human-to-animal and animal-to-human transmission of SARS-CoV-2

Several reports confirm human-to-animal transmission (reverse zoonosis). Infected animals had close contact with the RT-PCR-positive humans, suggesting that the virus was transferred in one direction (human-to-animal). Dogs, cats, wild felines (tigers and lions), and minks on fur farms were tested RT-PCR-positive,[3,191,199,209] a dog and cat even for a new variant SARS-CoV-2 B.1.1.7,[210] whereas farm animals like pigs, cows, chickens, and ducks (poultry), had not been reported RT-PCR-positive, and the risk of transmission from humans-to-bats was considered to be low.[211]

There is evidence of human-to-cat and human-to-dog[209] transmission of SARS-CoV-2 but so far not vice versa. One study suggested that cat fleas, *Ctenocephalides felis*, might act as biological and/or mechanical vectors, as coronavirus-derived RNA and cell receptor ACE RNA/proteins were identified in cat fleas.[212] However, current evidence suggests that pets are probably "dead-end"-hosts with small risk of transmission to humans. Still, pet owners are concerned: 60% of U.S. veterinarians encountered owners that were worried about their pets having COVID-19.[213]

There is also concern that cats or dogs could transmit SARS-CoV-2, although there is no evidence for zoonotic transmission so far.[214] Thus, owners in some countries started to abandon their pets, however, fear of potential transmission from domestic cats is unnecessary without solid proof of risk. On the contrary, according to computational modeling, abandoning domestic cats actually might cause even more people to be infected overall.[215]

6 | RECOMMENDATIONS OF THE EAACI TASK FORCE

The recommendations stated here are based on expert opinion after performing a narrative review of the actual literature. A systematic review using the GRADE system for definition of strong and conditional recommendatioins needs to be performed in the future when more data are available and when several knowledge gaps (Box 1) have been closed.

6.1 | Measures to prevent transmission of COVID-19

Fact 1: The transmission probability of SARS-CoV-2 including all its mutant versions between human-to-human is high and occurs via secretory fluids (nasal, oral, and lung).

Recommendation 1: By following regulations (eg, social distancing) and hygiene measures, people protect themselves and others from infection:

- Wearing mouth-nose-protection when meeting people outside own household
- Maintaining a safety distance of at least 1–2 meters to other people or animals
- Avoiding crowds and crowded places
- Regularly ventilating closed rooms
- Washing hands very carefully and regularly, either by using alcohol-based hand rub or soap and water before eating, before touching the face, after using the toilet, and after using public transport, public places, gym etc.
- Avoiding touching the face (eyes, nose, and mouth)
- Avoiding skin contact with people outside own household
- Covering mouth and nose with the inside of elbow or tissue when coughing or sneezing (cough etiquette)
- With fever, cough or difficulty of breathing, medical attention needs to be sought, according to the procedure recommended by the authorities
- Staying at home and self-isolating even with the mildest symptoms (cough, headache, and mild fever)
- When being tested positive, quarantine/self-isolation needs to be started immediately for 10–14 days
- Keeping up-to-date and informed by trusted sources like WHO, OIE, and national health authorities

TABLE 2 Characteristics of SARS-CoV-2 infection in different species

Species/animals	Entry receptor similarity	Experimental infection	Naturally infected	Symptoms reported naturally/experimental	Antibodies detected	References
BAT	Low	Unknown	Possible source of SARS-CoV-2	Unknown/unknown	Unknown	Damas et al[46] Liu et al[220]
LION	Not tested	Unknown	Yes	Mild/n.a.	Unknown	Damas et al[46] AVMA [221]
TIGER	Medium	Unknown	Yes	Mild/n.a.	Unknown	Damas et al[46] AVMA [221]
DOG	Low	Yes	Yes	No/n.a.	Yes	Damas et al[46] Shi et al[174]
CAT	Medium	Yes	Yes	Mild/no	Yes	Halfmann et al[208] Shi et al[174] Damas et al[46]
PANGOLIN	Very low	Unknown	Yes	Unknown/unknown	Unknown	Damas et al[46] Zang et al[218]
FERRET/MINK	Very low	Yes	Yes	Yes/yes	Yes	Oreshka et al[199] Shi et al[174] Damas et al[46]
HAMSTER	Medium	Yes	Unknown	Yes	Yes	Sia et al[184] Damas et al[46]
RHESUS MACAQUES	Very high	Yes	Unknown	Yes	Yes	Munster et al[183] Damas et al[46]

Abbreviation: n.a., not applicable.

BOX 1 Knowledge gaps/future research

Despite what was learned within the last decades about coronaviruses, and even more so within the last year, there are a number of remaining knowledge gaps regarding the latest SARS-CoV–2 infection

- First, it is not known what the original source or the intermediate hosts of SARS-CoV-2 are (Table 1). It is also not completely understood which transmission ways are relevant, neither for interspecies transfer for animals, nor cross-species-wise in a zoonotic way from animals to humans (which are relevant?), or reverse-zoonotic way (do infected humans pose a differing risk to different animal species in close proximity?)
- In all species, the efficacy of an established immune response against SARS-CoV-2 (eg, neutralizing antibodies) as well as its duration are not known, due to the short duration of the pandemic (1.5 years).
- Mutations of SARS-CoV-2 take place roughly every two weeks. More than 20 genetically stable mutations might have taken place already since the outbreak, however, for many the impact on the infectibility, transferability, disease severity, and treatment are not known, both for humans and animals.

Fact 2: Animal-to-animal transmission is possible, for example, between cats.

Recommendation 2: For animals/pets, there are guidelines given by several animal health organizations, like

- during lock-down or quarantine pets should not be allowed to interact with animals (and people) from other households;
- dog parks or public places, where it can be crowded, should be avoided.

Fact 3: Transmission from animals to humans (zoonosis) has not been proven yet. There are reports for transmission from humans to animals (reverse zoonosis), so cross-species transfer is possible. Humans should therefore be careful and maintain high hygienic standards for themselves and to protect the animals and prevent further interspecies transmission. The risk of SARS-CoV-2 mutants, which acquire new pathogenetic properties and could employ novel transmission routes, is always given.

Recommendation 3: If the *holder* is infected, hygienic measures are highly important to keep the pet safe (Box 2).

If the pet/companion/farm *animal* is SARS-CoV-2-infected, the holders also need to be careful to protect themselves and others (Box 2). Contact should be restricted to a minimum, interaction with others (pets or humans) should be avoided, hygienic measures are unavoidable until animals are RT-PCR-negative

Fact 4: Professionals who work with animals, like veterinary medical personnel, zoo keepers, or pet shop personnel, see their patients despite a pandemic.

BOX 2 Recommendations of the EAACI task force

Measures to prevent cross-species transfer

Humans should be careful and maintain high hygienic standards for themselves and to protect the animals and prevent further interspecies transmission

- Infected owners should wear mouth-nose-protection, also during food preparation for the animal; no eating or drinking should take place in close proximity to each other, including no sharing of foods or drinks, or bed.
- Infected owners should regularly wash and disinfect hands.
- Quarantine/isolation should also be applied to pets in the COVID−19-affected human families; pets should not interact with other people/animals from other households
- Other people should take care of the animal if holder is SARS-CoV−2-positive; if this is not feasible, keep distance from the animal as far as possible and wear mouth-nose-protection.
- If animals are tested positive, they should be kept away from other animals and humans, and public places or dog parks, where it can be crowded, should be avoided.
- Humans and their animals should not consume exotic animals, their meats, or products made thereof, especially if sold and kept in a clustered way under unsanitary conditions ("wet markets").

Recommendation 4: Veterinary clinics should have restricted access, where owners have to hand over the patients and are not allowed to accompany their pets to the examination. People who work with wildlife also have the responsibility to keep the animals' risk as low as possible. Strict hygienic measures must be taken to reduce contact to the absolute minimum, wear gloves while interacting, for example, petting, and wear a mask during food preparation and contact. The same measures should be taken in pet shops, and in addition, prevent

costumers from interacting with the animals, restrict the number of costumers inside the store, prevent direct contact to the animals. Zoos play a special role because they are crucial for species conservation. In this case, areas where endangered species live should be highly protected, maybe even closed for visitors. Caretaker and staff must follow the hygienic protocols and the animals' health should be monitored very closely for signs of possible SARS-CoV-2 infection.

6.2 | Concluding remarks

In times of climate change (eg, when changes in temperature and humidity influence reservoirs of viral infections, transmission by insects and other intermediate hosts, survival outside the host, and success of infection in plants and animals);changed living conditions (very close to companion animals and pets); and changed eating patterns (exotic animals and plants, animals fed with medications), pandemics could appear at any time.

The general public and health organizations need to be prepared and implement strategies (i) to detect and characterize novel threats early; (ii) to reduce the risk of transmission by initiating hygiene measures very early in suspicious diseases; (iii) to speed up the development of treatment (medications, vaccines) and prevention options; (iv) to educate on the risk of exotic foods, and (v) to stop the underlying reasons for pandemic evolution in the first place, for example, facilitate planetary health, implement climate protective measures, protect/re-establish biodiversity, take care that people have access to hygienic food and water and therefore (can) avoid consumption of unsanitary food and drinks. In this sense, prevention and management of pandemics need to be approached from a holistic point of view with One Health being the best strategy.

CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHORS CONTRIBUTIONS

KADJ authored text about transmission, animal models, and prepared figures and tables. JJ contributed part on horses, equine receptors, and porcine CoV. UE contributed chapter on symptoms associated with SARS-CoV-2 infection in human patients. SM wrote the chapter on SARS-CoV-2 receptors and associated proteins. FW wrote part on human symptoms in SARS-1 and MERS as well as allergic aspects. AI contributed to concluding remarks, scientific discussion and editing of the manuscript. SAA wrote parts about avian and bovine coronaviruses. HK wrote the parts on cats and dogs. J-JE contributed the part on human comorbidities. P-SI designed the concept of this position paper and directed the project, wrote abstract, knowledge gaps, position part, and edited paper and references. All authors have read and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Korath ADJ, Janda J, Untersmayr E, et al. One Health: EAACI Position Paper on coronaviruses at the human-animal interface, with a specific focus on comparative and zoonotic aspects of SARS-Cov-2. *Allergy*. 2021;00:1–17. https://doi.org/10.1111/all.14991